DETAILED ACTION

Amendment Entry

1. The amendment entered January 31, 2008 has been entered. Claims 1-4 and 6 have been amended. Claim 7 has been newly added. Claims 5 is cancelled. Claims 1-4, 6 and 7 are under consideration in this office action.

Withdrawal of Objections and Rejections

2. The following objections and rejections have been withdrawn in view of applicants' amendments:

a) The objection of claims 2-6;

b) The rejection of claims 1-6 under 35 U.S.C. 112, second paragraph,

c) The rejection of claims 1 and 3-6 under 35 U.S.C. 102(a) as being anticipated by Adelman et al, (1997. J. of Biol. Chem. Vol. 272(43): 27435-27443).

d) The rejection of claims 1-4 and 6 under 35 U.S.C. 102(b) as being anticipated by Pahari et al., (July 7,1997. FEBS Letters Vol. 411:60-62).

Response to Arguments

3. Applicant's arguments filed January 31, 2008 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The written description rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, is maintained.

Claim 1 is drawn to a method of identifying a ligand of a bacterial, sigma^{70} subunit which comprises contacting the sigma^{70} subunit or a portion thereof comprising the anti-sigma binding region, with a test compound and a GST-AsiA fusion protein produced in a yeast expression system; determining whether the test compound binds competitively with the AsiA-protein component of the fusion protein to sigma^{70} subunit or portion thereof; and identifying any such competitively binding test compound as a ligand of the bacterial s sigma^{70} subunit. Therefore the written description is not commensurate in scope with the claims drawn to any portion thereof.

Applicants' assert that the knowledge in the field at the time, when taken with the acknowledged disclosure in the instant specification, must be taken as confirmation that Applicants had possession of the invention at the time of filing. However, the specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. The specification teaches the structure of only a single representative species of such portions. The specification fails to describe any other representative species by any identifying characteristics or properties other than having the anti-sigma binding region. Given this lack of description of representative

species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants' urge that the specification and claims set out what portions can be used in the practice of the present invention. Therefore, the office invites Applicants to point out a sufficient number of representative species that encompass the portion thereof comprising the anti-sigma binding region genus. The rejection is maintained on the grounds that the genus has a substantial variance, therefore the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. MPEP 2163 states that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus.

While it is understood that the instantly claimed methods are based on the determination of competitive binding between a test compound and the AsiA protein to the sigma^{70} subunit; the portion thereof need have no other characteristic than containing the anti- sigma^{70} binding region for the claimed assay system to work; this understanding does not overcome the written description rejection. The rejection is maintained because neither the specification nor the claims teach how to define the portions thereof. Neither the claims nor the specification teach how to obtain such portions. There is no guidance as to what portions can or cannot be used in the method being claimed. Thus, the resulting portions thereof result in a complexes not taught by the specification.

Applicants' argue that the claims do not recite portions of the subunit which are mutants or variants. However, the genus of portions claimed is a large variable genus and including mutants and variants, which can have wide variety of structures as long as they comprise the anti-sigma binding region. Moreover, the specification fails to describe any representative species by any identifying characteristics or properties other than having the anti-sigma binding region. The disclosure of the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

In view of these considerations, a person skilled in the art would not have viewed the teachings of the specification sufficient to show that applicants were in possession of the claimed portions thereof comprising the anti-sigma binding region. Thus applicants' arguments are not persuasive and the written description rejection is maintained.

Response to Arguments

5. Applicant's arguments with respect to claims 1-4 and 6-7 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection Necessitated By Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms and abbreviations like GST-AsiA in claim 1 must be spelled out when used for the first time in a chain of claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3-4 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adelman et al, (1997. J. of Biol. Chem. Vol. 272(43): 27435-27443) in view of Voelker et al., (1996. J. of Bacteriology. Vol. 178(23): 7020-7023).

Claim 1 is drawn to a method of identifying a ligand of a bacterial, sigma^{70} subunit which comprises contacting the sigma^{70} subunit or a portion thereof comprising the anti-sigma binding region, with a test compound and a GST-AsiA fusion protein produced in a yeast expression system; determining whether the test compound binds competitively with the AsiA-protein component of the fusion protein to sigma^{70} subunit or portion thereof; and identifying any such competitively binding test compound as a ligand of the

bacterial s sigma^{70} subunit. Claim 3 is drawn to the sigma^{70} subunit or portion thereof is obtained from *Escherichia coli*. Claim 4 is drawn to the AsiA-protein component of the fusion protein has an amino acid sequence as shown in SEQ ID NO: 1. Claim 6 is drawn to the ligand being an inhibitor of a bacterial sigma^{70} subunit. Claim 7 is drawn to the fusion protein being produced in a *Saccharomyces cerevisiae* or *Pichia pastoris* expression system.

Adelman et al., teach the interaction of AsiA with both full-length sigma^{70}, and GSTσ(506) and measuring the fraction of AsiA bound to either sigma^{70} or GSTσ(506) (page 27,436, col. 2). Adelman et al., teach the test compound as being the AsiA protein. Adelman et al., teach contacting a glutathione-S-transferase (GST) GST-sigma^{70} fusion protein, containing GSTσ(506), the C-terminal 108 amino acids of sigma^{70}, fused to the GST moiety (page 27,436, col. 2). Adelman et al., teach a fusion protein of an anti-sigma^{70} factor of bacteriophage T4. Adelman et al., teach the determination of the competitive interaction between GSTσ(506), AsiA and sigma^{70} (page 27,436, col. 2). Adelman et al., teach the sigma^{70} is obtained from *E.coli* (abstract). Adelman et al., teach the anti-sigma^{70} factor having the full-length comprising the amino acid sequence as shown in SEQ ID NO: 1. Adelman et al., teach the AsiA protein is known as an inhibitor of the sigma^{70} subunit (page 27,435, col.2). However Adelman et al, do not teach a GST-AsiA fusion protein produced in a yeast expression system.

Voelker et al., teach the sigma fusion proteins produced in yeast reporter systems in *Bacillus subtilis* sigma^{B} regulator (page 7020). It is noted that the *B. subtilis*

gene expression of the sigma factors encoded by the *rsbW* genes is an example of proteins regulating the sigma subunit of RNA polymerase known in another, yet related system. Voelker et al., teach the cloning of coding sequences in *sigB* operon products into specialized plasmids to create translational fusions between these proteins and the separated modular domains (DNA binding domains and transcriptional activation) of the yeast transcriptional activator (page 7020). Voelker et al., teach the activation of a target promoter fused to an appropriate reporter gene, wherein the system is especially useful for detecting weak and transient protein interactions (page 7020). Voelker et al., teach the systems were commercially available and the clonings were performed according to the protocols (page 7020).

Therefore it would have been prima facie obvious at the time of applicants invention to modify the method of identifying a ligand of a bacterial, sigma^{70} subunit as taught by Adelman et al., wherein the modification exchanges the expression system of Adelman et al., for the yeast expression system of Voelker et al. in order to combine prior art elements according to known methods to yield predictable results from producing fusion protein in yeast expression systems. No more than routine skill would have been required to exchange the fusion protein producing system of Adelman et al, for a commercially available and functionally equivalent yeast system of Voelker et al, which are useful for cloning when examples of similar regulating the sigma subunit of RNA polymerase protein known in a related system, are amenable to production in yeast expression systems. Moreover, one of ordinary skill in the art would have a reasonable expectation of success by exchanging the expressions systems when the

art teaches that the commercially available yeast do not have the drawbacks associated with the use prokaryotic systems, since simple substitutions of one known equivalent element for another obtains improved predictable results.

Claim Rejections - 35 USC § 103

8. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adelman et al, (1997. J. of Biol. Chem. Vol. 272(43): 27435-27443) and Voelker et al., (1996. J. of Bacteriology. Vol. 178(23): 7020-7023) as applied to claim 1 above, and further in view of Pahari et al., (July 7,1997. FEBS Letters Vol. 411:60-62).

Claim 2 is drawn to the method comprising: (i) immobilizing the sigma^{70} subunit or portion thereof on a matrix or solid support; (ii) adding the test compound and the fusion protein; (iii) adding a first antibody against the fusion protein; (iv) adding a labeled second antibody against the first antibody; and (v) determining the amount of second antibody bound to the (first antibody- fusion protein-sigma^{70} subunit or portion thereof) complex formed on the matrix or solid support.

Adelman et al, and Voelker et al., have been discussed above, however neither teach: (i) immobilizing the sigma^{70} subunit or portion thereof on a matrix or solid support; (ii) adding the test compound and the fusion protein; (iii) adding a first antibody against the fusion protein; (iv) adding a labeled second antibody against the first antibody; and (v) determining the amount of second antibody bound to the (first antibody- fusion protein-sigma^{70} subunit or portion thereof) complex formed on the matrix or solid support.

Pahari et al., teach contacting the sigma^{70} subunit with a test compound and a fusion protein of an anti-sigma^{70} factor of bacteriophage T4, and determining whether the test compound binds competitively with the anti-sigma^{70} factor to the sigma^{70} subunit (page 61). Pahari et al., teach contacting *AsiA* complex with anti-sigma^{70} and anti-AsiA antibodies as the first antibody (page 61, Fig. 3). Pahari et al., teach contacting to each, a polyclonal antirabbit sigma^{70} antibody (the second antibody) for immunoprecipitation with Sepharose beads (the matrix or solid support) (page 61, Fig. 3). Pahari et al., teach the sigma^{70} subunit being obtained from *Escherichia coli* (page 60, col.1).

Therefore it would have been prima facie obvious at the time of applicants invention to modify the method of identifying a ligand of a bacterial, sigma^{70} subunit as taught by Adelman et al., and Voelker et al, wherein the modification uses an immobilization step and dual antibodies for determination the amount of bound antibody as taught by Pahari et al., in order to determine the binding ability of the components.

No more than routine skill would have been required to exchange the SDS-PAGE gel determination for the functionally equivalent western analysis methods which provides specific results despite the use of variant AsiA mutants. Moreover, one of ordinary skill in the art would have a reasonable expectation of success by exchanging the detection methods which both use SDS-PAGE techniques to create gels containing the interacted protein complexes yet the Western analysis provides for specific protein recognition giving huge advantages in terms of flexibility, and adds an amplification step to the detection process.

Conclusion

9. No claims allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/

Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645